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14. ABSTRACT

Despite administrative difficulties that delayed the initiation of the protocol parts involving human subjects, we were ready with all issues that did not involve human subjects, an accomplishment that enabled us to start the human testing immediately once the approval was achieved. To date, we are about to close the gap and will be able to perform the experiment as planed during the next few months. The initial pretests experiments are going very well. We have already performed the pre-test on 10 subjects. The pretest measurements will be compared to similar measurements after the treatment is completed (at posttest) in order to evaluate the accomplished improvement. Moreover, we start having initial results of training in healthy subjects, showing improvement if contrast sensitivity, both in the fovea and periphery. We will start to summarize initial post-test results next quarter. After receiving the first post-test results from the ongoing group, we plan to refine and test a slightly different training protocol in order to choose the optimal protocol for training the TBI patients.

15. SUBJECT TERMS
Traumatic Brain Injury; Perceptual Learning; Behavioral Treatment; Visual Dysfunction; Cortical Plasticity

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Introduction

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Different traumatic brain injuries are associated with visual dysfunction (Chua, Ng, Yap & Bok, 2007). Tissue damage following stroke, car accident, etc. may result in visual scotomas or other severe visual deficits. Accumulating evidence suggests that the adult visual cortex retains significant potential for experience-dependent plasticity (Fahle, 2002). A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. Plasticity is based on neuronal excitations and is affected by pharmacological changes in the balance between neuronal excitation or inhibition (He, Hodos & Quinlan, 2006, Maya Vetencourt, Sale, Viegi, Baroncelli, De Pasquale, O'Leary, Castren & Maffei, 2008, Rozas, Frank, Heynen, Morales, Bear & Kirkwood, 2001).

A method developed in our laboratory is a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations. Neuronal interactions in the visual processing were robustly affected by changes in the balance between excitations and inhibitions. We applied our paradigm to treat abnormal neuronal interactions in amblyopic adults (Polat, 2008, Polat, Ma-Naim, Belkin & Sagi, 2004). We were the first to show plasticity in adults with a visual deficit that was considered untreatable, see below. Using a similar paradigm, we also achieved a significant improvement in individuals with presbyopia, see below (Polat, 2009). Thus, our treatment induces visual enhancement of blurred or low-contrast images, an effect that is highly applicative for patients with visual dysfunction associated with TBI. We have a highly efficient and practical treatment technique to improve vision. Thus, we can apply this proved effective training techniques to evoke plasticity in the damaged visual cortex of patients with TBI. The training paradigm is intended to reduce the extent of the damaged visual fields (i.e., "restitution training").

Body

This section of the report shall describe the research accomplishments associated with each task outlined in the approved Statement of Work.

Below is the research accomplishments for the first task specified in the approved ***Statement of Work.***

Since the project has received the final approval for compliance with human subjects protection requirements only on Jul 30th 2011, a delay was posed on the stages of the study that involve human subjects. However, since we received the approval, we have started to recruit and test subjects very intensively, so we will close the gap during the next months. We have already performed the pre-test on 10 subjects. The pretest measurements will be compared to similar measurements after the treatment is completed (at posttest) in order to evaluate the accomplished improvement.

Other than the tasks involving human subjects, all tasks were completed.

Task 1. To apply behavioral training to healthy control individuals using our paradigm that is adapted for peripheral vision. This experiment will provide us with exact indications on potential effectiveness of the treatment and the amount of expected improvement in the target populations. (months 1-12):

1a. Modification of the software for periphery (months 1-2).

Was accomplished.

The training was adapted:

- Parameters were changed both within and between sessions
- The inter-flanker distance is made adjustable to the scotoma size

1b. Adapting the eye-tracking system for the new setup (months 3-4).

Was accomplished.

Custom-designed User Graphic Interface (GUI) to be used with the eye-tracking equipment was developed (Fig. 1). It will be used during:

- Pretest
- Posttest
- Progress evaluation sessions during the treatment

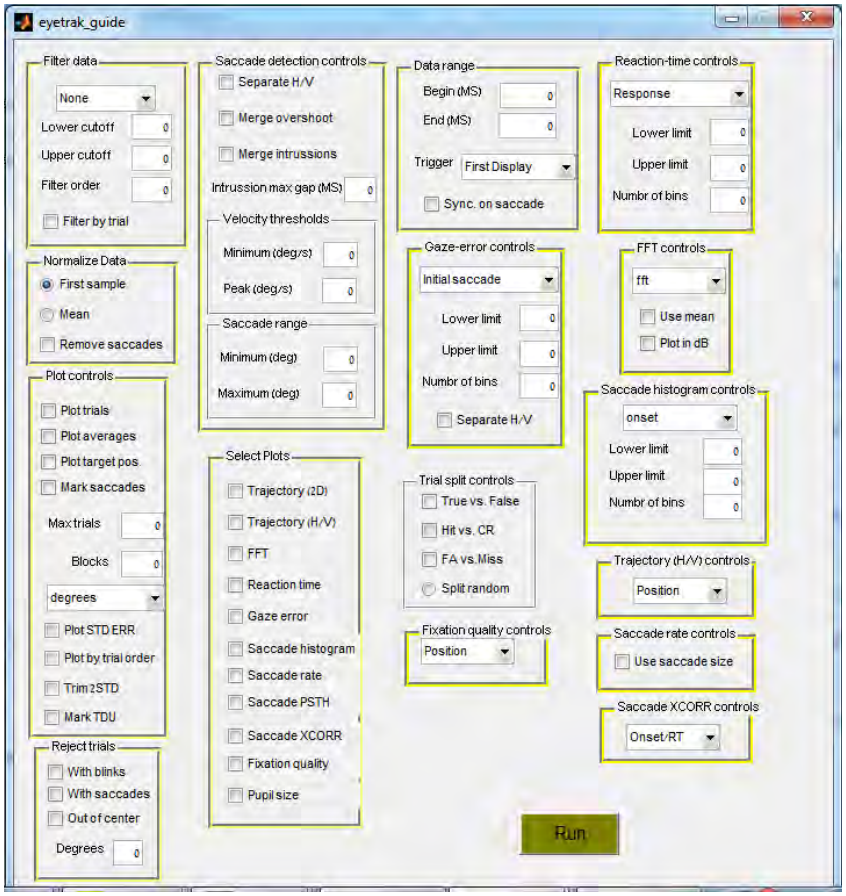

Figure 1 Custom-designed User Graphic Interface (GUI) to be used with the eye-tracking equipment.

1c. Creating of Matlab interface for interpretation of the eye-tracking results (months 3-4).

Was accomplished.

An example of the Eye tracking output is presented (Fig. 2). Blue – smooth pursuit to one of 8 radially placed targets; Red – microsaccades (small saccadic eye movements) during visual fixation.

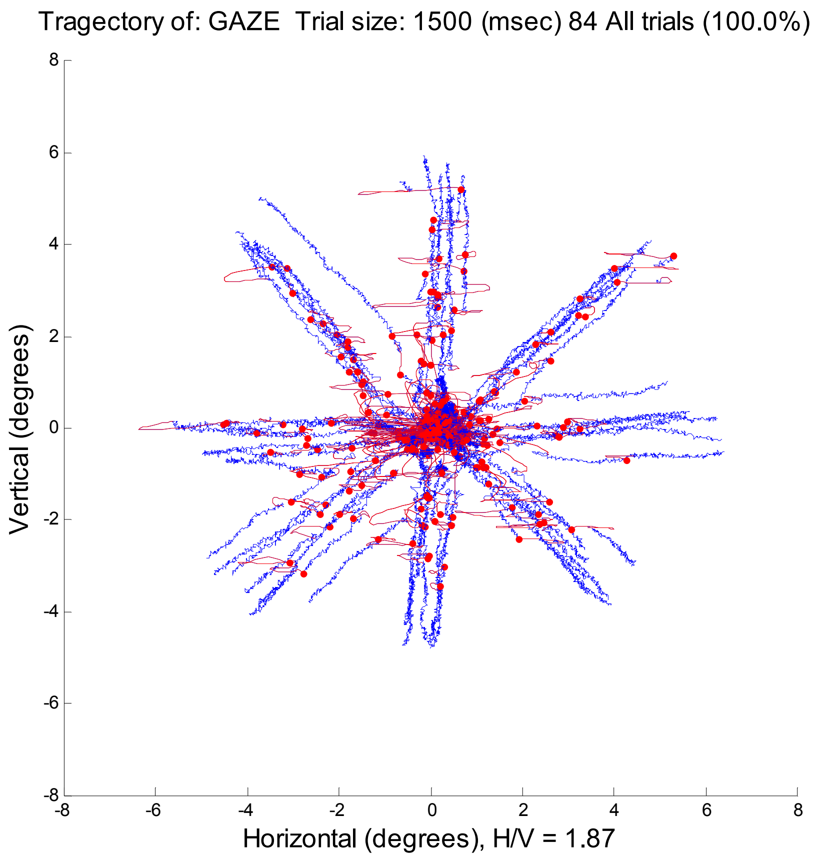

Figure 2 Example of the Eye tracking output.

1d. Healthy participants recruitment and screening (months 3-9).

Started recently, after approval for compliance with Human Subjects Protection requirements. On-going.

We have already recruited 10 subjects (i.e., half of the 20-subject group of healthy participants).

1.e Baseline testing of the healthy participants (3-9)

Started recently, after approval for compliance with human subjects protection requirements. On-going.

We have already recruited 10 subjects (i.e., half of the 20-subject group of healthy participants) that will enable evaluation of the results and modification of the training parameters, if necessary.

Preliminary testing results of the healthy participants are:

E-test – a computerized custom version of ETDRS test for visual acuity assessment (Bonneh, Sagi & Polat, 2007), separately in the fovea and in the periphery that is designated for treatment based on the visual field analysis. Preliminary results of 8 participants are presented (Fig. 3). Crowding was computed as the increase in the size of the minimal detected letter "E" compared to a single letter "E". Two inter-letter spacing were tested: 1 and 4 letters. Crowding in the periphery was measured relative to the results obtained in the fovea (i.e., normalized to the foveal measurements that provide a baseline with no crowding effect). A significantly higher crowding with the higher letter density (spacing of 4 letters) compared to the lower (spacing of 1 letter) is observed (p=0.005, paired t-test).

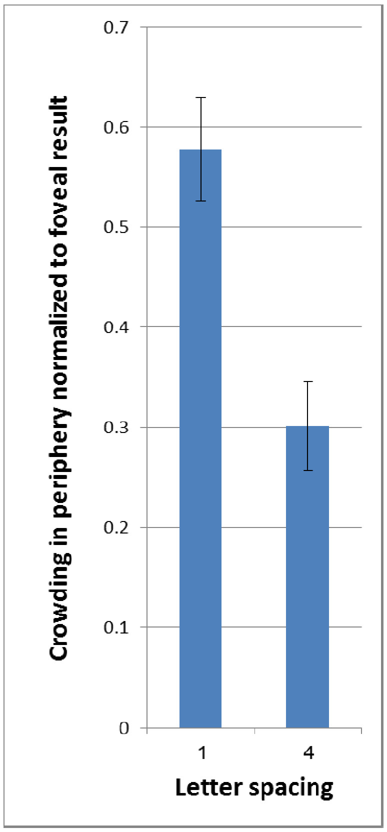

Figure 3 Crowding tested by E-test.

N=8; error bars, SEM.

Transient Contrast Sensitivity - a computerized custom version of Contrast Sensitivity test, probing detection for briefly presented Gabor targets (target presentation for 60 msec). Preliminary results of 9 participants are presented (Fig. 4). Performance (percent of correct responses) is presented in the fovea and in the periphery (at the eccentricity of 4 degrees) for several target contrasts. There are clear effects of the target contrast and of the eccentricity on contrast sensitivity. The results show a robustly lower in the periphery compared to the fovea. For instance, for the same target contrast of 10%, the percent of

correct responses in the fovea is above 90, whereas it is slightly above the chance level (60%) in the periphery.

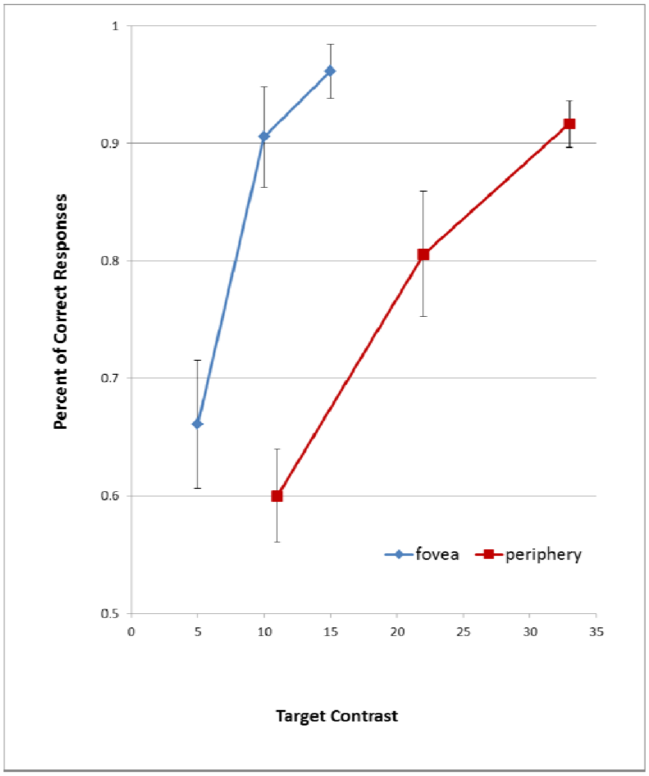

Figure 4 Percent of correct responses for different target contrasts in fovea and periphery. N=9; error bars, SEM.

Static Contrast Sensitivity - a computerized custom version of Contrast Sensitivity test, probing detection for statically presented Gabor targets (target presentation until response). Preliminary results of 8 participants are presented (Fig. 5). Detection threshold (contrast) is presented for "Day" and "Night" conditions, at 3 different spatial frequencies each. There are clear effects of the lightening conditions and of the spatial frequency on contrast sensitivity.

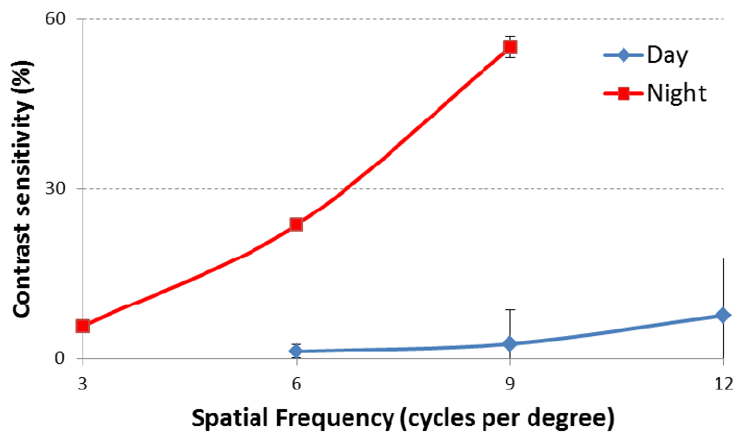

Figure 5 Static Contrast Sensitivity under Day and Night conditions for different spatial frequencies. N=8; error bars, SEM.

Stereo Acuity - a computerized custom version of Stereo Acuity test, probing the effect of spatial disparity (gap) between briefly presented two-line targets (targets presented for 1 second). Preliminary results of 7 participants are presented (Fig. 6). Stereo acuity is presented for different disparities. There is a clear effect of disparity on stereo acuity.

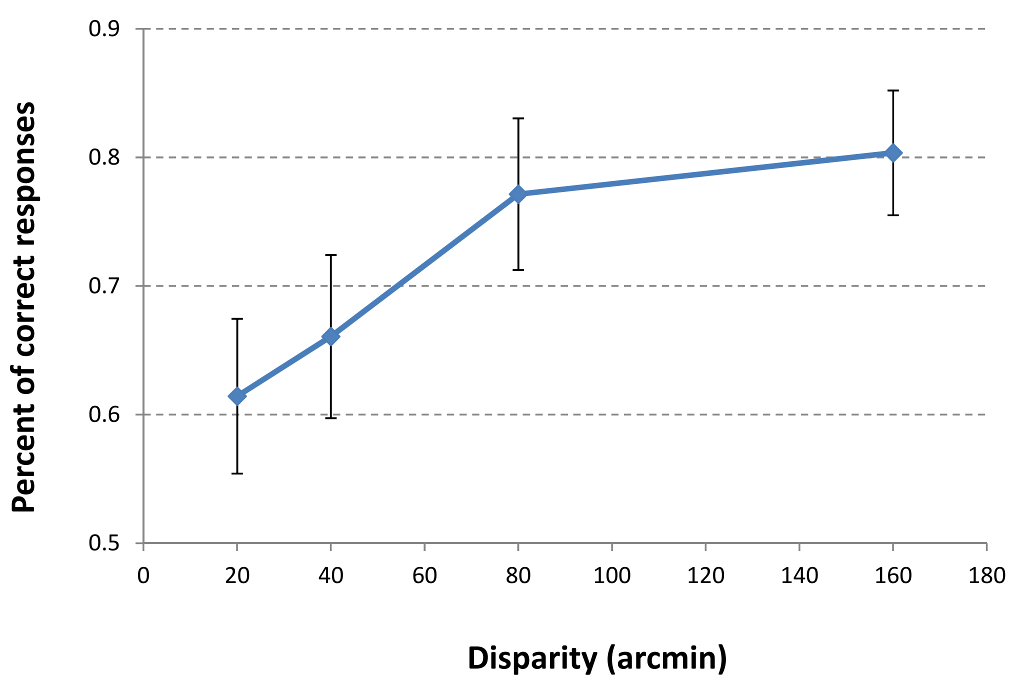

Figure 6 Stereo acuity for different spatial disparities. N=7; error bars, SEM.

Eye-tracking – recording of eye movements during a Transient Contrast Sensitivity task. Preliminary results for two representative subjects (SF and NL) are shown: the trajectories of

eye movement recorded from 1.5 meters (Figs. 7 and 8). The figures show, separately, the horizontal and vertical positions of the dominant eye, relative to the fixation point on the screen. The horizontal axis is the time relative to stimulus onset (the green bar shows the target duration, TDU). Results for correct (True) and wrong (False) responses are presented separately. Note that fixation of subject SF is more stable than of subject NL. For both subjects, there are no saccades away from fixation point during TDU, but there are some afterwards. Also, in the vertical eye position there are many eye blinks, but long after the TDU.

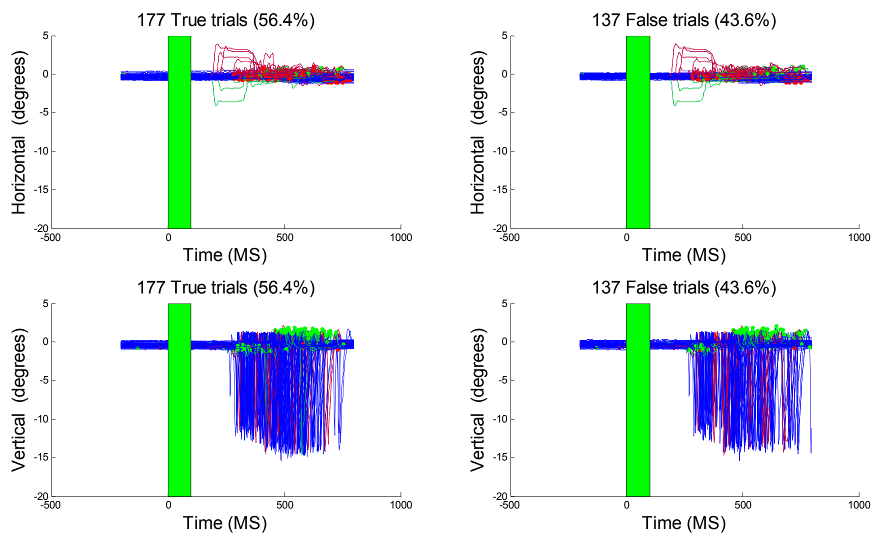

Figure 7 Eye tracking results for subject SF. The green bar shows the target duration.

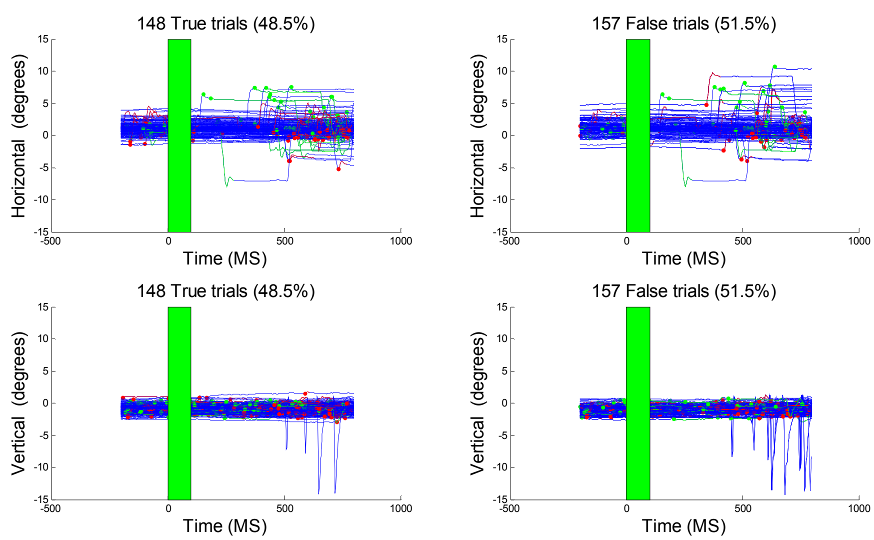

Figure 8 Eye tracking results for subject NL. The green bar shows the target duration.

1e. Training of the healthy participants (months 3-12).

Training of the healthy subjects was started recently, after approval for compliance with Human Subjects Protection requirements. On-going.

Preliminary training results of the healthy participants on a Transient Contrast Sensitivity task are shown below (Fig. 9). Percent of correct responses in the fovea and periphery are shown before (pretest) and after (posttest) completing 10 training sessions (each session on a different day). The contrast of the stimuli was 8% in the fovea and 18% in the periphery (factor 2.25). The results show that whereas before training the percent of correct responses in the fovea was slightly above the chance level and below the chance level in the periphery, after 10 training sessions it reached a 100% level both in the fovea and periphery.

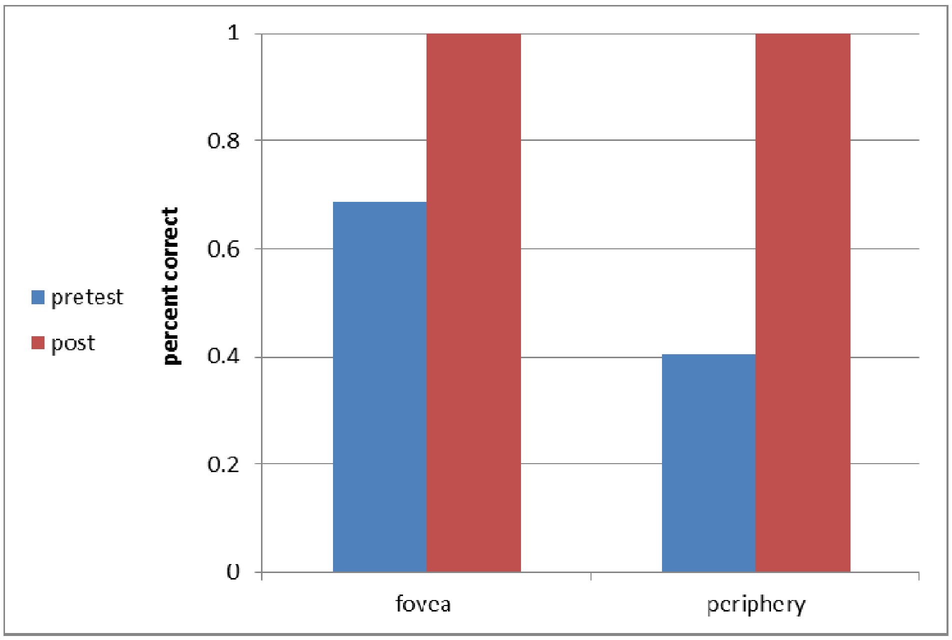

Figure 9 ***Preliminary training results of a representative healthy subject.***

1.e Post-treatment testing of the healthy participants (6-12)

Was not started yet. Will be performed during the next quarter for the first sub-group (10 subjects).

1f. Data analysis and summary of the first year of the project (months 9-12).

Not relevant yet. Will be performed during the next year.

Key Research Accomplishments

Bulleted list of key research accomplishments emanating from this research.

Reportable Outcomes

- PLR Meeting presentation, 12 Apr 2011.
- Accomplishment of the technical, administrative and technological (programing) tasks required to initiate the experiments.
- Validation of the pretest testing.
- Recruitment of research assistance for managing the training sessions.
- Starting screening the medical files to identify potential TBI patients.

Conclusion

Despite administrative difficulties that delayed the initiation of the protocol parts involving human subjects, we were ready with all issues that did not involve human subjects, an accomplishment that enabled us to start the human testing immediately once the approval was achieved. To date, we are about to close the gap and will be able to perform the experiment as planed during the next few months. The initial pretests experiments are going very well and we will start to have initial post-test results next quarter. After receiving the first post-test results from the ongoing group, we plan to refine and test a slightly different training protocol in order to choose the optimal protocol for training the TBI patients.

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